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Progress report

Peptide absorption in man

In this review it is hoped to trace the evolution of our concepts of the absorption of digestion products of dietary protein. Many of the ideas current today were readily accepted by the end of the last century but were ignored by orthodox physiologists during the first half of this century—concepts of sugar absorption suffered a similar fate. Although it has now become clear that brush border hydrolysis and consequent utilization of the sugar pump is the predominant method of sugar absorption it would seem that two major mechanisms are involved in peptide absorption: on the one hand hydrolysis of peptides by brush border enzymes with subsequent uptake of the liberated amino acids by specific amino acid transport systems, and on the other hand, uptake of peptides by mechanisms independent of the specific amino acid entry mechanisms, followed by intracellular hydrolysis.

Historical Background

Nineteenth century physiologists believed that dietary protein was absorbed in the form of polypeptides[1,2,3], a view that seemed to be confirmed when Nolf[4] and Messerli[5] showed that 'peptones' produced by tryptic hydrolysis of protein disappeared from the lumen of the small intestine more rapidly than equivalent amounts of free amino acids. When Cohnheim demonstrated in 1901[6] that 'intestinal juice' was capable of hydrolysing peptones to amino acids, some early workers suggested that protein must be hydrolysed to amino acids before absorption took place. This hypothesis began to gain ground when all known free amino acids were detected in intestinal contents obtained during protein absorption *in vivo*[7,8,9], and when studies *in vivo* showed that hydrolysates of protein (consisting of amino acids) disappeared rapidly from the lumen of the small intestine[10,11]. Furthermore, many of the investigators at the time speculated that free amino acids passed into the portal circulation during protein absorption as the non-protein nitrogen values in peripheral and portal plasma increased during absorption of amino acids[12,14], protein hydrolysates, and whole protein[15,16]. When only amino acids were isolated from the portal circulation during protein absorption[17], the idea that protein was completely hydrolysed to amino acids within the intestinal lumen before absorption took place became the classical view of protein absorption (eg, Verzar and MacDougall, 1936[18]). This view was held despite later observations that intraluminal peptidase activity was insufficient to account for the absorption of 'peptone' in the form of free amino acids[19].

The concept was questioned by a number of workers who claimed that peptides entered the portal venous circulation during protein absorption[20,22]. The quantitative significance of their findings was unknown, and later studies, using improved techniques, failed to detect an increase in peptide-bound amino acid levels in portal plasma during protein absorption[23-27]. The final vindication of the classical view of protein absorption appeared to be provided

by the demonstration, using ion exchange chromatography, that only free amino acids appeared in peripheral plasma after protein was administered to human subjects[28].

In 1954 Fisher strongly criticised the classical view of protein absorption[29]. He pointed out that it had previously been shown that upwards of 200 hours were required for the liberation of 90% of the amino acids from different proteins subjected to successive action of pepsin, trypsin, and erepsin[30,31], and made the following statement '. . . even on the most generous assumption, the time course of liberation of amino nitrogen is too slow to fit with the view that protein must be digested to amino acids before they are absorbed', and he suggested that the idea of absorption of protein in the form of peptides deserved serious consideration[29].

Mucosal Uptake of Oligopeptides

Initial experiments *in vitro* with dipeptides showed that small quantities of intact glycyl-glycine and glycyl-L-leucine crossed the intestinal wall[32]. Similar observations were made when glycyl-glycine was studied *in vitro*[33–35] and *in vivo*[35] by other workers, and after Newey and Smyth[36] demonstrated that dipeptides could be taken up intact by intestinal mucosa they concluded[37] that the products of protein digestion could be transported into the mucosal cell in the form of oligopeptides as well as amino acids. The concept of intact peptide uptake as a second mode of protein absorption, although not disputed was not thought to be quantitatively significant[38], as it seemed much more likely that absorption of peptides, analogous to disaccharides[39–42], would involve brush border hydrolysis with subsequent absorption of the released amino acids by amino acid transport systems.

The modern era of our knowledge of peptide absorption stemmed from the results of oral load experiments carried out by Matthews and his colleagues in man[43,44]. They found that a given quantity of glycine was absorbed faster when administered orally as the dipeptide and tripeptide than in the free form. The authors concluded that the peptides must have been taken up intact by the intestinal mucosa because, if analogous to disaccharide absorption, brush border peptide hydrolysis preceded amino acid transport; when presented initially, the liberated amino acids could not have been absorbed more rapidly than in the free form. Similar findings, subsequently confirmed in the rat[45], have been demonstrated in man when a perfusion technique was used to study diglycine[46–48,49] and triglycine absorption[48].

When the absorption of mixed peptides of glycine and methionine and the corresponding amino acids was studied in the rat[50,51] it was found that glycine was absorbed at a slower rate from an equivalent mixture of glycine and methionine than from a solution containing only free glycine. This competition for transport between the two amino acids was abolished when glycyl-methionine and methionyl-glycine were presented, and in addition, both amino acids were absorbed faster from the peptides than from the equivalent amino acid mixture. If brush border peptide hydrolysis preceded amino acid uptake, competitive phenomena would not be avoided, and these findings were cited as further evidence in favour of the presence of a specific peptide uptake system. Although not an invariable finding[52], similar results have been

obtained in man when absorption of a number of other mixed peptides composed of neutral amino acids has been studied (glycyl-leucine[46], glycyl-alanine [47,53,54], and alanyl-glycine[53]).

Recently a large survey *in vitro* showed that the uptake of one or both constituent amino acids by rat intestine was greater from 18 out of 22 dipeptides containing basic and acidic amino acids than from the equivalent amino acid or amino acid mixtures[55]. These findings have been confirmed in man for glycyl-L-lysine but not for L-lysyl-L-lysine[56].

After Matthews and his colleagues had implied that oligopeptides are transported intact into the mucosal cell by special peptide uptake systems in normal human subjects[43,44], Milne and his colleagues showed that patients with Hartnup absorbed the amino acids histidine, tryptophan, phenylalanine, and tyrosine normally when they were given in the form of the respective dipeptides carnosine[52], glycyl-tryptophan[57], phenylalanyl-phenylalanine[57], and glycyl-tyrosine[58], but not when they were administered in the free form. In cystinuria the loss of active transport of arginine is also adequately compensated by peptide uptake systems[59], although loss of active transport of free lysine seems to be compensated by the presence of passive or facilitated diffusion mechanisms[60], in addition to peptide uptake[56].

Nutritional Importance of Oligopeptide Uptake in Man

The studies carried out in Hartnup disease[52,57,58] and cystinuria[56,60] emphasize the nutritional importance of oligopeptide transport in these two conditions. Although the present experimental data suggest that in normal subjects peptide uptake may play a more important part in protein absorption than had previously been suspected[61,63], only 15 oligopeptides have so far been studied in man. In view of the fact that there are about 400 possible dipeptides and 8000 possible tripeptides, it would clearly be impossible to assess the overall nutritional importance of peptide absorption by studying the characteristics of absorption of each one in turn. Nixon and Mawer[64,65] studied the absorption of small quantities of milk protein and gelatine in man and concluded that although appreciable amounts of the basic amino acids (arginine and lysine) and neutral amino acids (valine, phenylalanine, tyrosine, methionine, and leucine) were released within the intestinal lumen at sufficient rates to account for their absorption in the free form, other amino acids (glycine, proline, hydroxyproline, serine, threonine, aspartic acid, and glutamic acid) were likely to be absorbed in the form of peptides.

Additional evidence has been provided by a recent perfusion study in man to support a concept that mucosal uptake of small peptides has an important or possibly a major role in protein absorption[66,67]. In agreement with initial studies carried out in the rat[68-69] total absorption of α amino nitrogen was greater from a solution containing an enzymic hydrolysate of casein, consisting mainly of oligopeptides of 2-6 amino acid units, than from the corresponding amino acid mixture of identical amino acid composition. In addition, there was less variation in the extent to which individual amino acids were absorbed from the peptide solution compared with that from the amino acid solution. This could result in enhanced protein synthesis, and the authors concluded, as had others[64,65,70], that the characteristics of absorption of amino acid mixtures are not representative of absorption of protein digestion products.

Mechanisms Involved in the Mucosal Uptake of Oligopeptides

One of the main difficulties in defining the nature of uptake mechanisms is that most peptides are hydrolysed rapidly by mucosal peptidases making it difficult to detect unhydrolysed peptide in the mucosal cell. *In-vitro* studies with the dipeptides glycyl-sarcosine[71] and carnosine[72], both of which are hydrolysed abnormally slowly by the mucosal cell, indicate that dipeptides may be transported by an active sodium-dependent process.

An important question that arises when considering the details involved in peptide transport is whether peptides are taken up by the same mechanisms that are responsible for the uptake of amino acids or whether independent peptide uptake systems exist as in bacteria[73,74]. Studies with glycine peptides seemed to indicate that amino acids and dipeptides shared a common entry site into the mucosal cell[37,44]. Parsons proposed an alternative scheme that dipeptides are taken up by attachment to adjacent amino acid entry sites, attachment and hydrolysis being different aspects of the same process[75]. Both schemes would appear to account for absorption of an 'affected' amino acid presented as a mixed peptide in Hartnup disease[52,57,58] and cystinuria[56,60]. Neither scheme, however, can explain the normal uptake of phenylalanyl-phenylalanine in Hartnup disease[57] or lysyl-lysine uptake in cystinuria[55]. An alternative explanation was thus proposed, that peptides are transported by mechanisms independent of amino acid transport[57]. Many recent *in-vitro* studies support the latter explanation[71,72,73,77] as uptake of a specific dipeptide is inhibited by the presence of other dipeptides but not by the presence of the constituent amino acids in the free form. Edwards postulated that there may be at least two independent dipeptide uptake systems in mammalian gut[78]. A single report[72] supports this hypothesis as carnosine uptake was not inhibited by lysyl-lysine or by glutamyl-glutamic acid, and in view of the fact that lysyl-lysine uptake was not inhibited by glutamyl-glutamic acid the authors proposed that independent peptide uptake systems exist for neutral, basic, and acidic dipeptides.

With the possible exception of glycyl-glycine[46,79] and hydroxyproline peptides[80], oligopeptides do not pass forward into the portal circulation. The precise site of peptide hydrolysis within the mucosal cell has not yet been defined. Ugolev and his colleagues[81–84] have proposed that oligopeptides as well as oligosaccharides[85] are hydrolysed at the external surface of the microvillous membrane by enteric and adsorbed enzymes, a process which is followed by transport of the monomer hydrolytic products across the membrane. In support of this concept Fern *et al* concluded from a kinetic study of uptake *in vitro* of mixed glycine and leucine peptides that hydrolysis of these peptides was entirely superficial[86], and the detection of free amino acids in the gut lumen during dipeptide absorption in animals[45,50,51] and man[46,48,53,54,56] would be readily explained if superficial peptide hydrolysis preceded amino acid uptake. The finding that oligopeptides confer a kinetic advantage on amino acid absorption, and the avoidance of competitive phenomena when oligopeptides are presented, suggests, however, that uptake of intact oligopeptides precedes cellular hydrolysis. The appearance of small quantities of glycyl-glycine in portal blood during absorption of this dipeptide[35,79], and the finding of intact dipeptides in the intestinal mucosa *in vitro*[71,72,88] certainly favours an intracellular hydrolysis site; additional evidence for this hypothesis is provided by cell fractionation studies which show that up to

90% of the total mucosal cell dipeptidase activity is localized to the cytosal fraction[87-90].

Matthews and his colleagues[51,61], as a result of kinetic studies *in vitro* with glycine and methionine peptides and the effects of L-amino acid oxidase on peptide uptake, suggested that there may be two modes of uptake of amino acids from oligopeptides: (1) peptide entry into the mucosal cells by a special mechanism, followed by intracellular hydrolysis; (2) surface hydrolysis by mechanisms closely linked to the amino acid entry mechanisms. Silk and his colleagues, who studied absorption of N-terminal glycine and alanine dipeptides in man[53,91], reached similar conclusions (see fig). On the one hand,

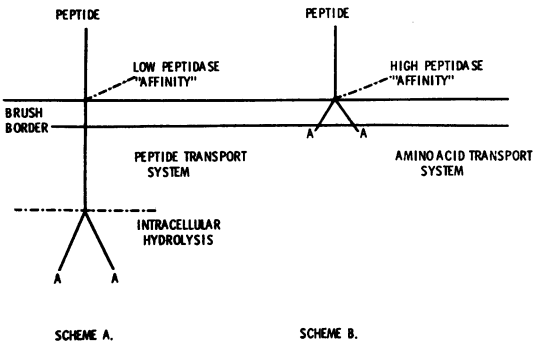

Fig *Postulated mechanisms for peptide uptake in man*

(scheme A) they proposed that dipeptides are transported into the mucosal cell by special entry mechanisms followed by intracellular hydrolysis as originally proposed by Newey and Smyth[37] which would explain their results with N-terminal glycine dipeptides. On the other hand, the results with N-terminal alanine dipeptides were more readily explained if dipeptide uptake involved both direct peptide entry (scheme A) and absorption of free amino acids, liberated as a result of brush border hydrolysis, by the specific amino acid transport systems (scheme B). They concluded[53] that the relative importance of either system was dictated by the affinity of the peptide for the superficial peptide hydrolases, although it is likely that further quantitative and qualitative assessments of enzymes in the human small intestine are needed before further conclusions can be drawn.

Practical Importance of Oligopeptide Transport

The demonstration that dietary protein is absorbed in the form of oligopeptides as well as amino acids explains why patients with Hartnup disease and cystinuria have no clinical signs of protein malnutrition, and the theoretical knowledge gained from investigations into peptide absorption may be expected to have important practical applications, especially in the treatment of protein malnutrition in seriously ill patients who have a reduced absorptive capacity of the small intestine. As it has been found that (*a*) greater absorption of α amino nitrogen, and (*b*) more even uptake of individual amino acids occurs from enzymic hydrolysates of protein than from equivalent mixtures of

free amino acids, the oral administration of mixtures of free amino acids in the treatment of such patients is likely to be less satisfactory than the oral administration of enzymic hydrolysates of proteins which consist of oligopeptides as well as free amino acids.

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